REMARKS

Amendments

Claim 1 is amended to provide the origin of the PAS acronym; claim 2 is amended to adopt the grammar suggested by the Examiner. These amendments do not alter the scope or meaning of the claims, and introduce no new matter.

35USC112, first paragraph (written description)

PAS domains are one of the most well-studied and documented protein domains, subject to thousands of scholarly publications. The Specification teaches and exemplifies the claimed methods with a wide variety of suitable PAS domains including PAS kinase PAS A, NPAS2 PAS A, HIF2a PAS B, HIF1a PASB, ARNT PAS B and HERG terminal PAS (p.6, lines 3-5; p.14, line 8 - p.21, line 10). Those skilled in the art recognize in the Specification a description of the claimed method of detecting binding of a PAS domain with a foreign core ligand. The practitioner does not require a description of the atomic structure or amino acid sequence of every or any targeted PAS domain to practice the invention.

35USC112, second paragraph

The claims are definite to one skilled in the art, as detailed below and documented in the attached expert Declaration.

(a) The origin of the PAS acronym is provided by amendment. PAS domains are one of the most well-studied and documented protein domains, subject to thousands of scholarly publications. While there is sequence variability across disparate PAS domains, those skilled in the art appreciate what is, and what is not a PAS domain, recognize the term PAS domain as definite, and recognize its metes and bounds.

(b) A foreign ligand of a PAS domain is distinct from a natural ligand naturally associated with the PAS domain in its host. This is consistent with our Specification which defines the foreign ligand as "not a natural ligand of the PAS domain" (e.g. p.4, lines 22-23) and "foreign to the [PAS domain] host." (e.g. p.5, line 24). One skilled in the art can discern what is, and what is not, a foreign ligand of a PAS domain, recognizes the term "foreign ligand" of a PAS domain

as definite, and recognizes its metes and bounds.

(c) The claims require that the recited PAS domain "comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity." This clause is literally self-explanatory to one skilled in the art, meaning literally that the core has no NMR-apparent a priori ("before experience") formed ligand cavity. This clause distinguishes and excludes those cores that have an NMR-apparent a priori formed ligand cavity. One skilled in the art can discern what is, and what is not, an "NMR-apparent a priori formed ligand cavity of a PAS domain hydrophobic core", recognizes the clause as definite, and recognizes its metes and bounds.

(d) The claims require comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. This step is literally self-explanatory to one skilled in the art, requiring literally that the practitioner compare the first NMR spectrum (in the presence of the ligand) with the second NMR spectrum of the PAS domain (in the absence of the ligand) to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. The step literally requires that the practitioner compare the NMR spectra to infer the presence of specific ligand binding. Details and examples of how the practitioner infers the presence of specific ligand binding from compared NMR spectra are provided, *inter alia*, at p.13, line 29 - p.21, line 10. In the context of our disclosure, one skilled in the art can readily discern what it means "to infer the presence of the ligand specifically bound", recognizes the phrase as definite, and recognizes its metes and bounds.

(e) The functionally equivalent grammar suggested by the Examiner is provided by amendment.

35USC103(a)

Fesik (WO97/18471) discloses the use of particular two-dimensional $^{15}N/^{1}H$ NMR correlation spectra to identify ligands of target biomolecules. Fesik teaches nothing about PAS domains.

Edery (US 5,843,683) characterizes four PAS domain containing proteins (AHR, SIM, ARNT and PER) and use co-immunoprecipitation experiments to propose that PAS domains

engage in PAS-PAS interactions. Edery proposes and claims assays for molecules that modulate PAS-PAS interactions.

Takahashi (US 6,291,429) describe circadian clock genes from humans and mice, and proposes contemplated uses of CLOCK polypeptides including use "in a screening assay for the identification of drugs or compounds that inhibit the action of CLOCK polypeptide (e.g., DNA binding)." Takahashi, col.9, lines 13-27.

Berkenstam (US 6,436,654) discloses and claims methods for identifying compounds which modulate the function of a functional domain of a variant of human HIF-1.alpha that lacks at least one functional domain thereof.

Our claims are specifically directed to a method of detecting binding of a PAS domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity. The method specifically requires the steps of: (a) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and (b) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

As explained in our Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification, p.1, line 22 - p.2, line 1. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5. Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores

with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the art (*supra*) teaches squarely away from such use.

Though the cited art does not support a prima facie case for obviousness, for good measure we provide affirmative evidence documenting the fact that one skilled in the art would have considered the claimed invention nonobvious at the time it was made (attached expert Declaration).

Nonstatutory Double Patenting

A terminal disclaimer over US Patent No. 6,319,679 is attached.

The Examiner is invited to call the undersigned with any suggestions for amending the claims or further clarifying any of the foregoing. Please charge our Deposit Account No.19-0750 (order UTSD:1510) all necessary fees, including extensions of time, or credit any overcharges relating to this communication.

Respectfully submitted,
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Encl. 132 Declaration
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